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(54) MEDICAL COMPOSITION

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a medical composition that has excellent biocompatibility, promptly and strongly hardens and can retain a suitable level of flexibility even after hardening, and to provide a method for producing the same.
SOLUTION: This medical composition comprises a first solution containing a linear polysaccharide derivative bearing succinimide residual group on the side chain and a second solution containing a polyamine and they are mixed to form gel.

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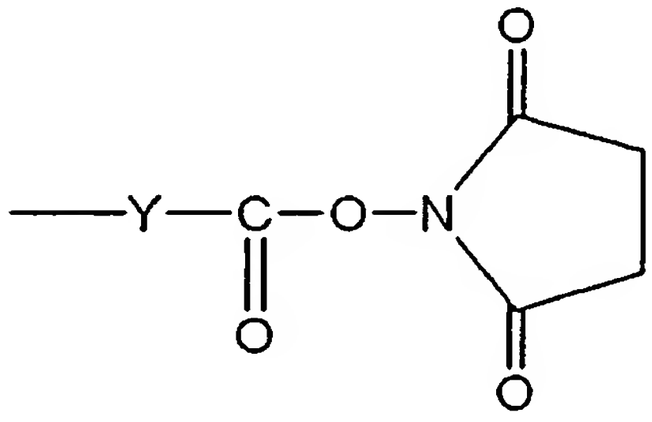
[Date of requesting appeal against examiner's decision of rejection]
[Date of extinction of right]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

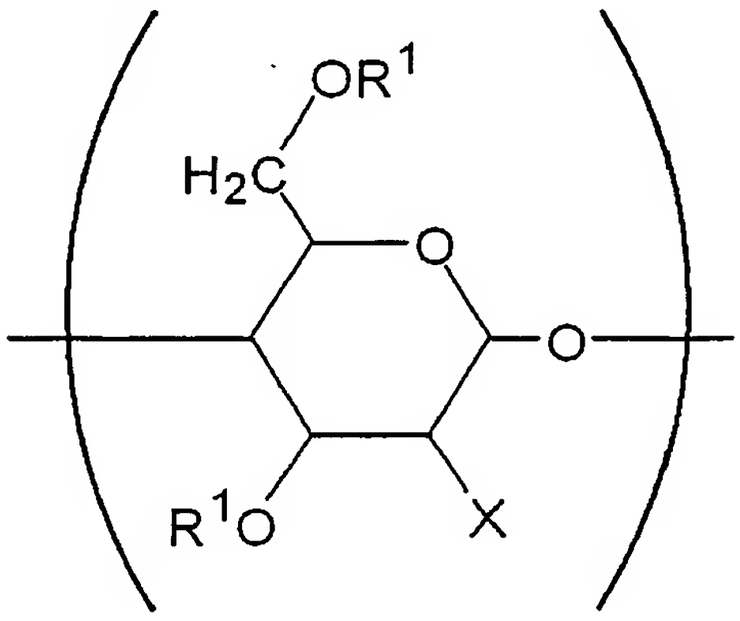
CLAIMS

[Claim(s)]
[Claim 1]
The medical-application constituent gelled by both mixing including the 1st liquid containing the chain-like polysaccharide derivative which introduced succinimide residue into the side chain, and the 2nd liquid containing polyamine.
[Claim 2]
Amount with the sufficient chain-like polysaccharide derivative which introduced succinimide residue into the side chain to cause gelation for the hydrogen atom of the hydroxyl group of a polysaccharide molecule by the reaction with said polyamine, the following type (I) :
[Formula 1]



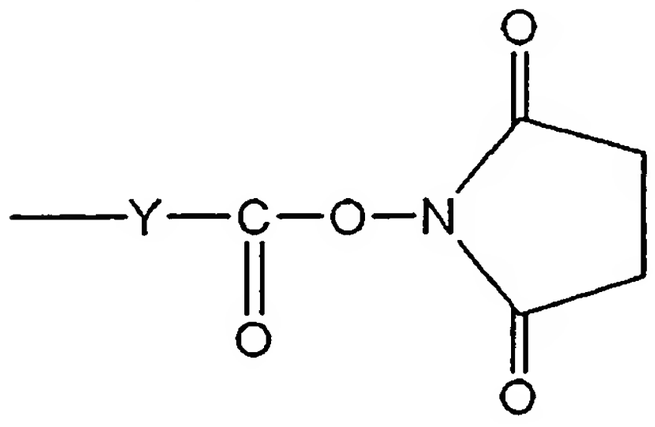
(I)

(-- Y expresses among a formula the alkylene or the carbamoyl group which may be permuted.)
-- medical-application constituent according to claim 1 which is the thing which it comes to permute by the succinimide content radical expressed.
[Claim 3]
The chain-like polysaccharide derivative which introduced succinimide residue into the side chain is the following formula as main structure (II). :
[Formula 2]



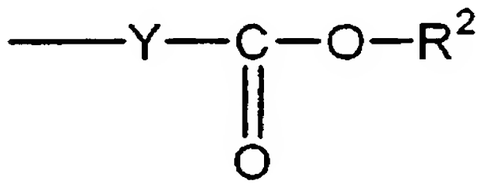
(II)

Inside of [type,
R1 is the aliphatic hydrocarbon, the aromatic hydrocarbon, or the following type by which a hydrogen atom, a metal atom, a carbon number 1, or 30 may be permuted (I). :
[Formula 3]



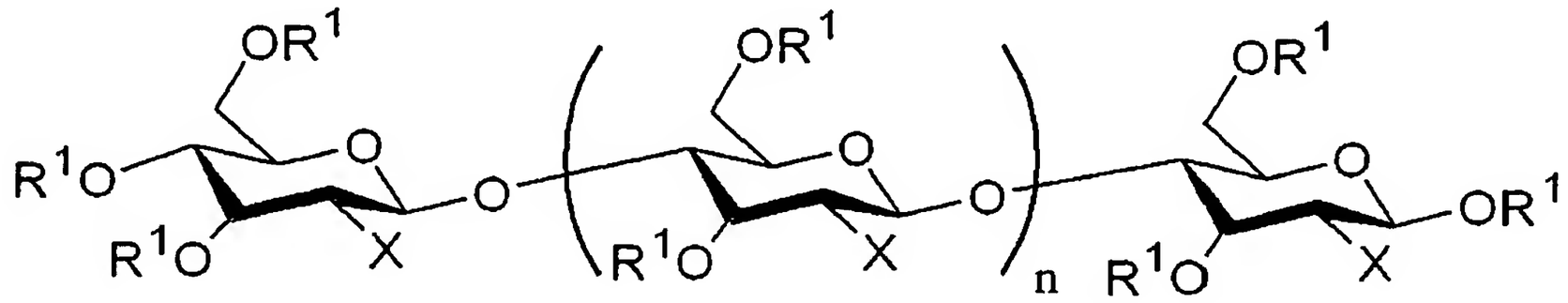
(I)

(-- Y expresses among a formula the alkylene or the carbamoyl group which may be permuted.) -- succinimide content radical or following formula (III): expressed
[Formula 4]



(III)

(-- Y is as having given the definition above among a formula, and R2 expresses the aliphatic hydrocarbon or aromatic hydrocarbon with which a hydrogen atom, a metal atom, a carbon number 1, or 30 may be permuted.) -- the radical expressed -- it is
X is -OR1, -NHR1 (R1 is the same as the above-mentioned definition among a formula.), or a carbamoyl group,
Although R1 in a molecule may be the same respectively or you may differ, at least one of them is the succinimide content radical of said formula (I).] The medical-application constituent according to claim 2 which is the sugar chain included as a repeat unit.
[Claim 4]
The main structures of the chain-like polysaccharide derivative which introduced succinimide residue into the side chain are the following formulas (IV). :
[Formula 5]

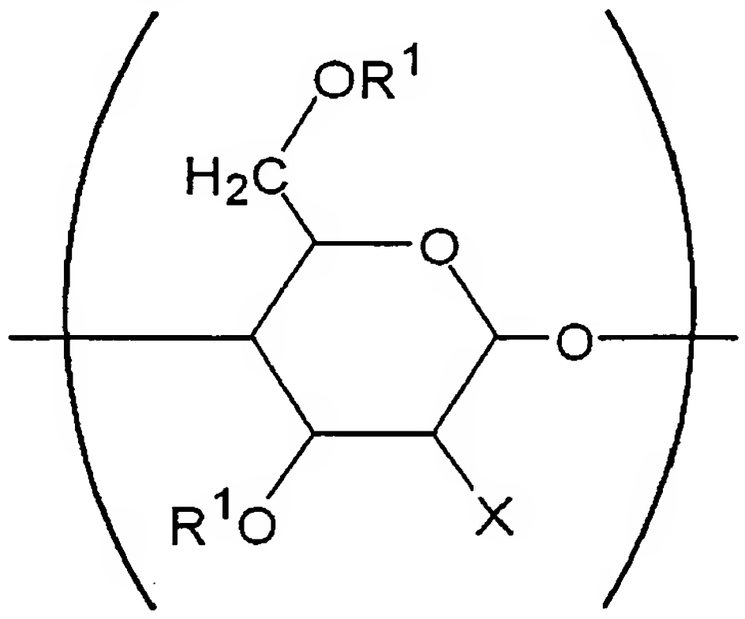


(IV)

(-- R1 and X are as said definition among a formula, and n is three or more integers.) -- medical-application constituent according to claim 3 which is the straight chain-like derivative expressed.
[Claim 5]
Said Y in a chain-like polysaccharide derivative is a carbon number 1 thru/or the alkylene of 3, or the following formula (V). :
[Formula 6]

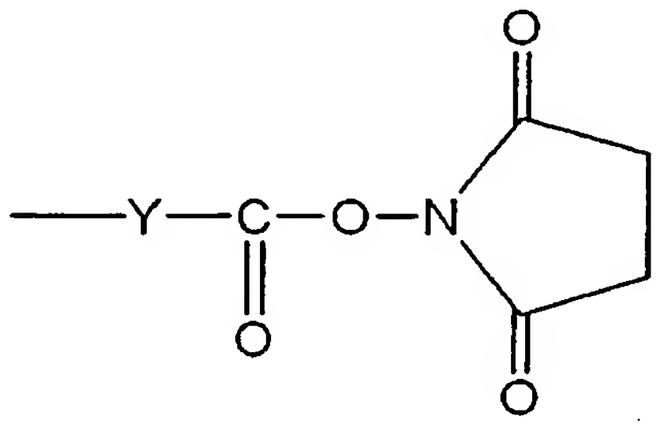
(V)

(-- R3 expresses among a formula the aliphatic hydrocarbon or aromatic hydrocarbon with which a hydrogen atom or a carbon number 1 thru/or 30 may be permuted.) -- medical-application constituent according to claim 2 to 4 which is the radical expressed.
[Claim 6]
The medical-application constituent according to claim 2 to 5 with which a chain-like polysaccharide derivative contains the succinimide content radical of said an average of 0.01 or more formulas (I) in each repeat unit.
[Claim 7]
The medical-application constituent according to claim 1 to 6 from which a chain-like polysaccharide derivative removes the impurity of low molecular weight by dialysis.
[Claim 8]
The medical-application constituent according to claim 1 to 7 whose polyamine is polyamine which has an amino group in a side chain.
[Claim 9]
Medical-application gel which mix, and claim 1 thru/or the chain-like polysaccharide derivative and polyamine of a medical-application constituent of 8 are made to react, and is obtained.
[Claim 10]
The gelation approach which makes an object side one side of the 2nd liquid containing the 1st liquid containing the chain-like polysaccharide derivative which introduced succinimide residue into the side chain, or polyamine with **, and covers an object side top with gel for the liquid of another side ** and by being dropped subsequently to said object side.
[Claim 11]
The adhesion approach on which make into the 1st object side with ** one side of the 2nd liquid containing the 1st liquid containing the chain-like polysaccharide derivative which introduced succinimide residue into the side chain, or polyamine, contact both and the liquid of another side is made to gel subsequently to the 2nd object side after being dropped, ** and, and the 1st and 2nd object side is pasted up.
[Claim 12]
The following type (II) :
[Formula 7]



(II)

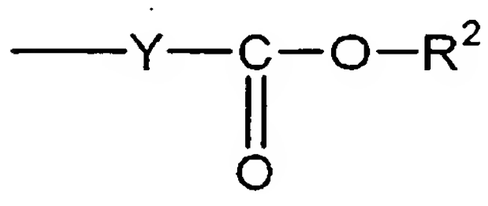
Inside of [type,
R1 is the aliphatic hydrocarbon, the aromatic hydrocarbon, or the following type by which a hydrogen atom, a carbon number 1, or 30 may be permuted (I). :
[Formula 8]



(I)

(-- Y expresses among a formula the alkylene or the carbamoyl group which may be permuted.) -- succinimide content radical or following formula (III): expressed

[Formula 9]



(III)

(-- Y is as having given the definition above among a formula, and R2 expresses the aliphatic hydrocarbon or aromatic hydrocarbon with which a hydrogen atom, a metal atom, a carbon number 1, or 30 may be permuted.) -- the radical expressed -- it is

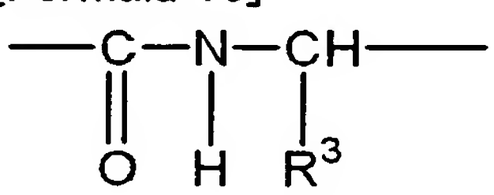
X is -OR1, -NHR1 (R1 is the same as the above-mentioned definition among a formula.), or a carbamoyl group,

R1 in a molecule may be the same respectively, or you may differ, and at least one of them is the succinimide content radical of said formula (II).] The sugar chain derivative included as a repeat unit.

[Claim 13]

Said Y in a chain-like polysaccharide derivative is a carbon number 1 thru/or the alkylene of 3, or the following formula (V). :

[Formula 10]



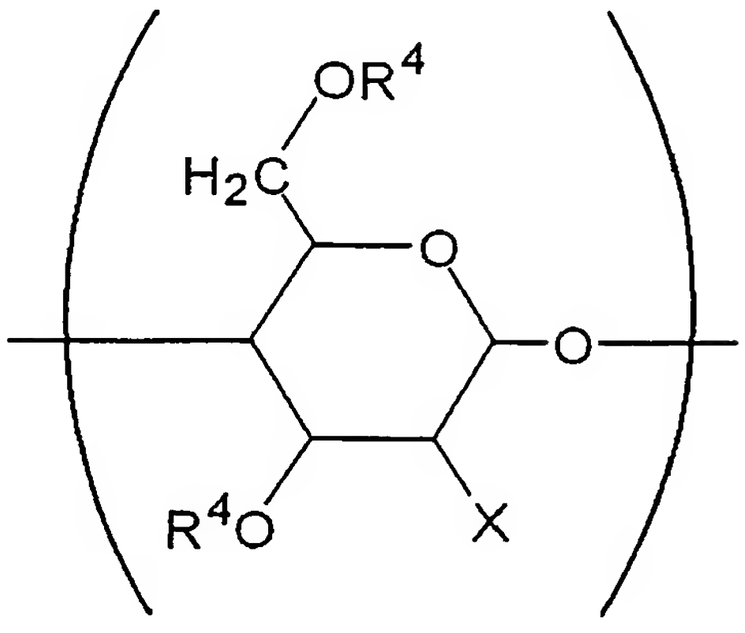
(V)

(-- R3 expresses among a formula the aliphatic hydrocarbon or aromatic hydrocarbon with which a hydrogen atom or a carbon number 1 thru/or 30 may be permuted.) -- sugar chain derivative according to claim 12 which is the radical expressed.

[Claim 14]

The following type (VI) :

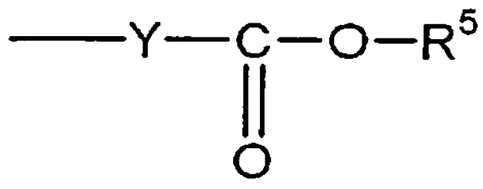
[Formula 11]



(VI)

R4 [come out, have the repeat unit expressed and] of at least one molecule is the following formula (VII). :

[Formula 12]



(VII)

(-- Y expresses among a formula the alkylene or the carbamoyl group which may be permuted, and R5 is a hydrogen atom or a metal atom.) -- the manufacture approach of a sugar chain derivative including making N-hydroxysuccinimide react to the sugar chain derivative expressed.

[Claim 15]

The manufacture approach of a sugar chain derivative according to claim 14 that a reaction is performed in an aquosity medium and the dialysis after a reaction removes the impurity of low molecular weight.

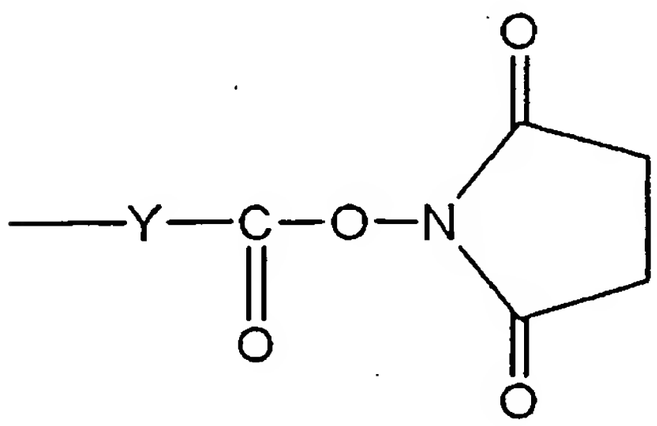
[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]
This invention relates to the sugar chain derivative which is the major component of this constituent, and its manufacture approach at the gelation and the adhesion approach using a medical-application constituent useful as a medical-application constituent especially the adhesives for hemostases, the charge of an antiadhesive material, wound covering material, etc., medical-application gel, and this constituent, and a list.
[0002]
[Description of the Prior Art]
**** produced in the living body, especially the blood vessel at the time of an operation and wounded, damage, and a joint -- insurance -- it is necessary to block certainly and quickly The piece of a synthetic fiber was used as assistance at the time of a suture or anastomosis, or the gelation ingredient has been used for such a purpose.
[0003]
The hemostasis ingredient which fabricated this is indicated using the collagen of the shape of a natural fiber doing a biochemical hemostatic action so as a piece of a synthetic fiber (for example, patent reference 1). However, the resolvability in the living body of the collagen of the shape of a natural fiber is low, and foreign body reaction may occur by remaining for a long period of time. Then, enzyme processing or the atelocollagen which alkali treatment is carried out, and antigenic is reduced and is obtained is also used in an antigenic determinant (for example, patent reference 2 and 3). However, since these atelocollagen has weak hemostasis nature, if a bridge is not constructed in addition to re-fibrosis, it is difficult to make it detain without making it dissolve in a fixed period until it carries out hemostasis, and the living body. However, there is a report of the atelocollagen which added bridge formation to reinforcement having low biocompatibility, and discovering inflammatory (nonpatent literature 1).
[0004]
As a gelation ingredient, most medical-application gel ingredients used as current, adhesive, and a hemostat use biomaterials (fibrinogen, gelatin, collagen, etc.) called the bone and hide of people's plasma protein, a cow, or a pig as a raw material, and it is manufactured. For example, the patent reference 4 is indicating the hemostasis for living bodies thru/or the tissue adhesives containing the hardening component which uses as a principal component the sizing agent component and aldehydes which use as a principal component the collagen protein partial hydrolysis matter and polyhydric-phenol compound which were sterilized by ethylene oxide. Here, the collagen protein partial hydrolysis matter is gelatin or glia. However, there is a possibility that a hepatitis virus, pyrogen, allergen, bovine spongiform encephalopathy (BSE), etc. may generally be contained in the living body origin ingredient, and the replacement to other ingredients [concern / over an infectious disease etc.] is desirable.
[0005]
Then, the adhesive and the hemostat by chemosynthesis which were manufactured without using the raw material originating in the body or an animal are also examined. For example, the water

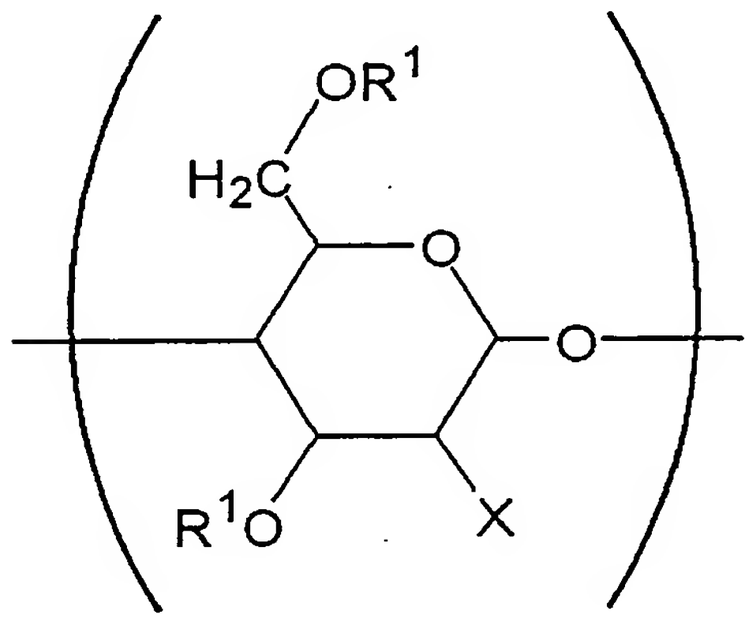
bloating tendency polymer gel which becomes the intramolecular used for the patent reference 5 as a cross linking agent of the salt of the straight chain diamine of specific structure from the polysaccharide which has a carboxyl group is indicated. Alginate or hyaluronate is mentioned as polysaccharide which has a carboxyl group, and N-hydroxysuccinic acid imide salt is mentioned as a salt of straight chain diamine.
[0006]
Moreover, the gelation approach which constructs a bridge over the patent reference 6 by the polyamine of specific structure in the compound made to come to react to the polysaccharide which has a carboxyl group with carbonyldiimidazole, carbonyl triazole, iodation chloro methyl pilus JIRIUMU (CMP-J), hydroxy benzotriazol, p-nitrophenol p-nitrophenyl trifluoroacetate, N-hydroxysuccinimide, etc. is indicated. Although the carboxymethyl cellulose is also mentioned to this official report as a polysaccharide which has a carboxyl group, the charge of a medical-application binder using the carboxymethyl cellulose equipped with the property which can be carried out is not specifically indicated. Moreover, only straight chain diamine is indicated as polyamine.
[0007]
Although only the ingredient of a cyanoacrylate system and a polyethylene-glycol system is put in practical use at the present stage as a chemical composition, application remains in what was restricted very much from the constraint based on the engine performance and toxicity.
[0008]
[Patent reference 1]
JP,6-339483,A
[Patent reference 2]
JP,6-197946,A
[Patent reference 3]
JP,8-196614,A
[Patent reference 4]
JP,10-314294,A
[Patent reference 5]
Patent No. 3107726
[Patent reference 6]
** table No. 529549 [2002 to]
[Nonpatent literature 1]
Koide et al.,Journal of Biomedical Materials Research,27(1)(1993)p.79-87
[0009]
[Problem(s) to be Solved by the Invention]
Therefore, this invention is excellent in biocompatibility, is hardened quickly and powerfully, and aims at moreover offering the medical-application gelation ingredient which holds suitable flexibility after hardening, and its manufacture approach.
[0010]
[Means for Solving the Problem]
this invention persons came to complete a header and this invention for the medical-application gelation ingredient containing the chain-like polysaccharide derivative which introduced succinimide residue into the side chain, and polyamine, as a result of inquiring in order to solve the above-mentioned trouble.
[0011]
That is, this invention provides the gelation which used the following medical-application constituents, medical-application gel, and this constituent and the adhesion approach, and a list with the sugar chain derivative which is the major component of this constituent, and its manufacture approach.
[0012]
[1] The medical-application constituent gelled by both mixing including the 1st liquid containing the chain-like polysaccharide derivative which introduced succinimide residue into the side chain, and the 2nd liquid containing polyamine.

[2] Amount with the sufficient chain-like polysaccharide derivative which introduced succinimide residue into the side chain to cause gelation for the hydrogen atom of the hydroxyl group of a polysaccharide molecule by the reaction with said polyamine, the following type (I) :
[Formula 13]



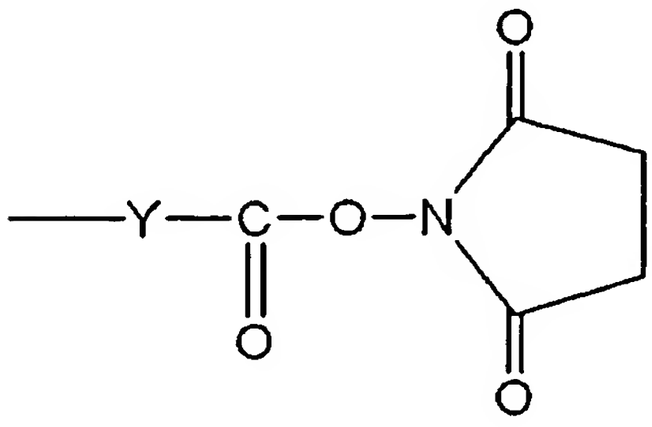
(I)

(-- Y expresses among a formula the alkylene or the carbamoyl group which may be permuted.)
-- medical-application constituent given in said 1 which is the thing which it comes to permute by the succinimide content radical expressed.
[0013]
[3] The chain-like polysaccharide derivative which introduced succinimide residue into the side chain is the following formula as main structure (II). :
[Formula 14]



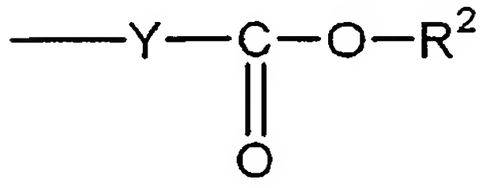
(II)

Inside of [type,
R1 is the aliphatic hydrocarbon, the aromatic hydrocarbon, or the following type by which a hydrogen atom, a metal atom, a carbon number 1, or 30 may be permuted (I). :
[Formula 15]



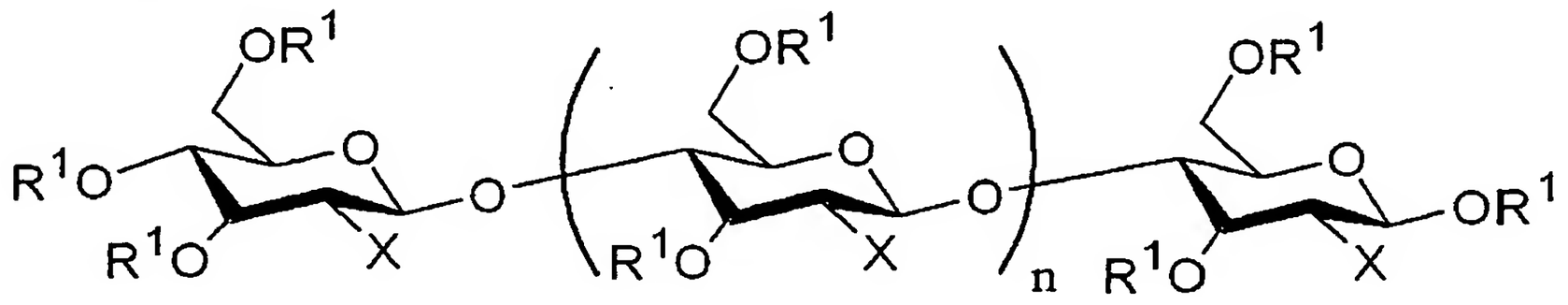
(I)

(-- Y expresses among a formula the alkylene or the carbamoyl group which may be permuted.)
-- succinimide content radical or following formula (III): expressed
[Formula 16]



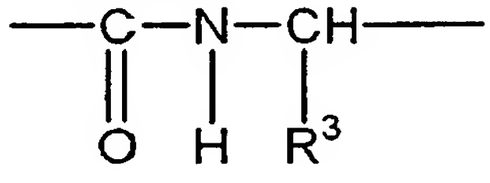
(III)

(-- Y is as having given the definition above among a formula, and R2 expresses the aliphatic hydrocarbon or aromatic hydrocarbon with which a hydrogen atom, a metal atom, a carbon number 1, or 30 may be permuted.) -- the radical expressed -- it is
X is -OR1, -NHR1 (R1 is the same as the above-mentioned definition among a formula.), or a carbamoyl group,
Although R1 in a molecule may be the same respectively or you may differ, at least one of them is the succinimide content radical of said formula (I).] A medical-application constituent given in said 2 which is the sugar chain included as a repeat unit.
[0014]
[4] The main structures of the chain-like polysaccharide derivative which introduced succinimide residue into the side chain are the following formulas (IV). :
[Formula 17]



(IV)

(-- R1 and X are as said definition among a formula, and n is three or more integers.) -- medical-application constituent given in said 3 which is the straight chain-like derivative expressed.
[5] Said Y in a chain-like polysaccharide derivative is a carbon number 1 thru/or the alkylene of 3, or the following formula (V). :
[Formula 18]

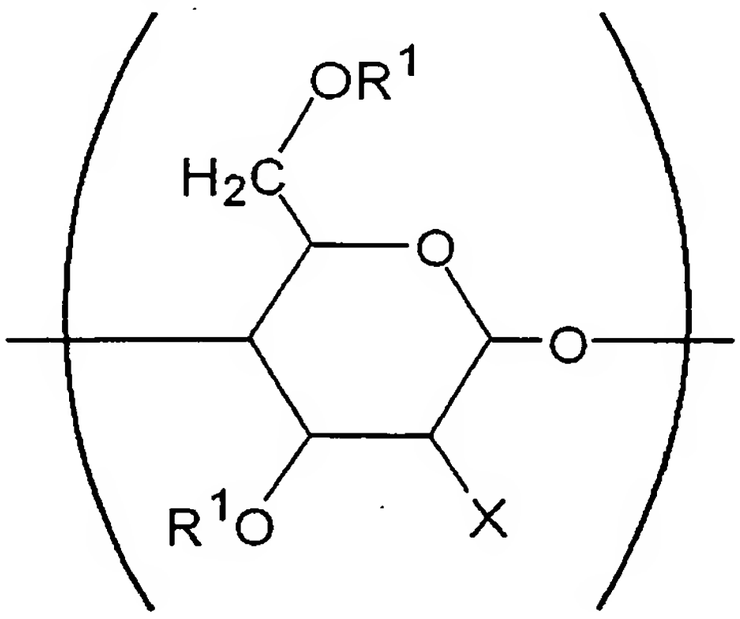


(V)

(-- R3 expresses among a formula the aliphatic hydrocarbon or aromatic hydrocarbon with which a hydrogen atom or a carbon number 1 thru/or 30 may be permuted.) -- medical-application constituent given in either [which is the radical expressed / said] 2 thru/or 4.
[0015]
[6] A medical-application constituent given in either [to which a chain-like polysaccharide derivative contains the succinimide content radical of said an average of 0.01 or more formulas (I) in each repeat unit / said] 2 thru/or 5.
[7] A medical-application constituent given in either [from which a chain-like polysaccharide derivative removes the impurity of low molecular weight by dialysis / said] 1 thru/or 6.
[8] A medical-application constituent given in either [whose polyamine is polyamine which has an amino group in a side chain / said] 1 thru/or 7.
[9] Medical-application gel which mix, and said chain-like polysaccharide derivative and polyamine of a medical-application constituent of 1 thru/or 8 are made to react, and is obtained.

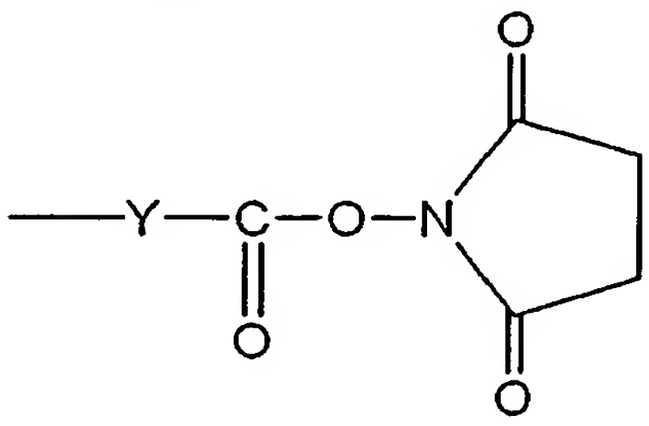
[0016]
[10] The gelation approach which makes an object side one side of the 2nd liquid containing the

1st liquid containing the chain-like polysaccharide derivative which introduced succinimide residue into the side chain, or polyamine with **, and covers an object side top with gel for the liquid of another side ** and by being dropped subsequently to said object side.
[11] The adhesion approach on which make into the 1st object side with ** one side of the 2nd liquid containing the 1st liquid containing the chain-like polysaccharide derivative which introduced succinimide residue into the side chain, or polyamine, contact both and the liquid of another side is made to gel subsequently to the 2nd object side after being dropped, ** and, and the 1st and 2nd object side is pasted up.
[0017]
[12] The following type (II) :
[Formula 19]



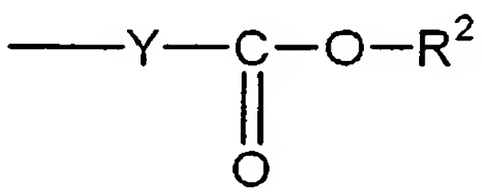
(II)

Inside of [type,
R1 is the aliphatic hydrocarbon, the aromatic hydrocarbon, or the following type by which a hydrogen atom, a carbon number 1, or 30 may be permuted (I). :
[Formula 20]



(I)

(-- Y expresses among a formula the alkylene or the carbamoyl group which may be permuted.)
-- succinimide content radical or following formula (III): expressed
[Formula 21]



(III)

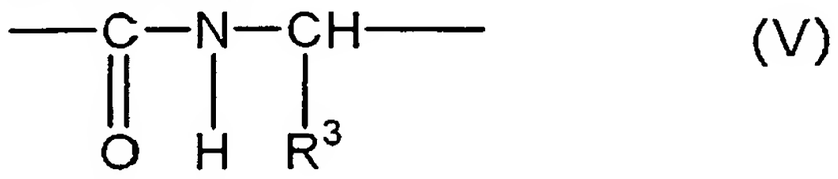
(-- Y is as having given the definition above among a formula, and R2 expresses the aliphatic hydrocarbon or aromatic hydrocarbon with which a hydrogen atom, a metal atom, a carbon number 1, or 30 may be permuted.) -- the radical expressed -- it is
X is -OR1, -NHR1 (R1 is the same as the above-mentioned definition among a formula.), or a carbamoyl group,

R1 in a molecule may be the same respectively, or you may differ, and at least one of them is the succinimide content radical of said formula (II).] The sugar chain derivative included as a repeat unit.

[0018]

[13] Said Y in a chain-like polysaccharide derivative is a carbon number 1 thru/or the alkylene of 3, or the following formula (V). :

[Formula 22]



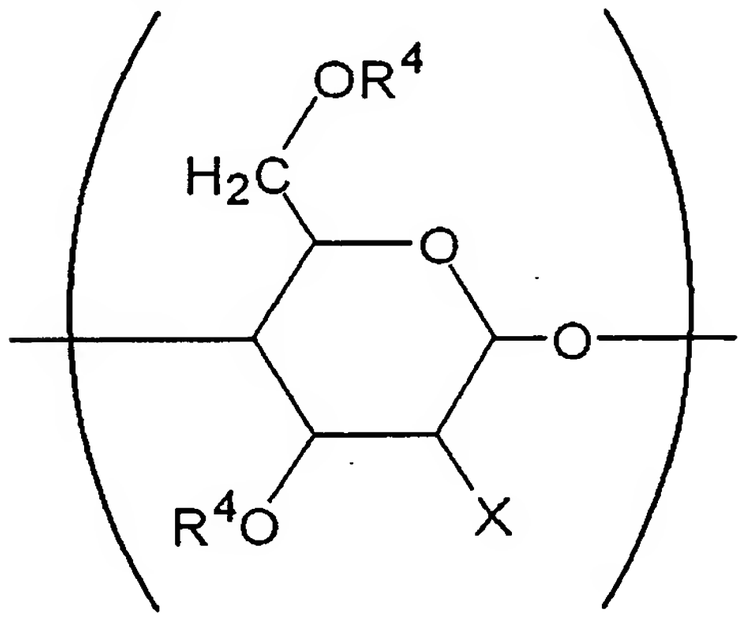
(V)

(-- R3 expresses among a formula the aliphatic hydrocarbon or aromatic hydrocarbon with which a hydrogen atom or a carbon number 1 thru/or 30 may be permuted.) -- sugar chain derivative given in said 12 which is the radical expressed.

[0019]

[14] The following type (VI) :

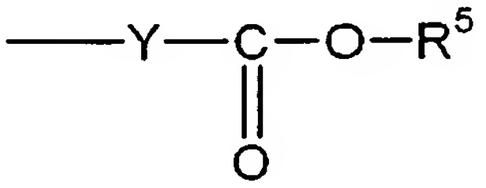
[Formula 23]



(VI)

R4 [come out, have the repeat unit expressed and] of at least one molecule is the following formula (VII). :

[Formula 24]



(VII)

(-- Y expresses among a formula the alkylene or the carbamoyl group which may be permuted, and R5 is a hydrogen atom or a metal atom.) -- the manufacture approach of a sugar chain derivative including making N-hydroxysuccinimide react to the sugar chain derivative expressed.

[15] The manufacture approach of a sugar chain derivative given in said 14 which a reaction is performed in an aquosity medium and removes the impurity of low molecular weight by dialysis after a reaction.

[0020]

[Embodiment of the Invention]

The medical-application constituent of this invention is an ingredient containing the chain-like polysaccharide derivative component which introduced succinimide residue into the side chain, and a polyamine component, and at the time of use, both components are mixed, reaction hardening is carried out, and it achieves functions, such as adhesion. In addition, in this

specification, "the charge of a binder" points out the ingredient for pasting an organization in such semantics and protecting this including adhesion of the organization which dissociated "adhesion", adhesion of not only anastomosis but an organization, junction, covering, reinforcement, a blockade, etc.

[0021]

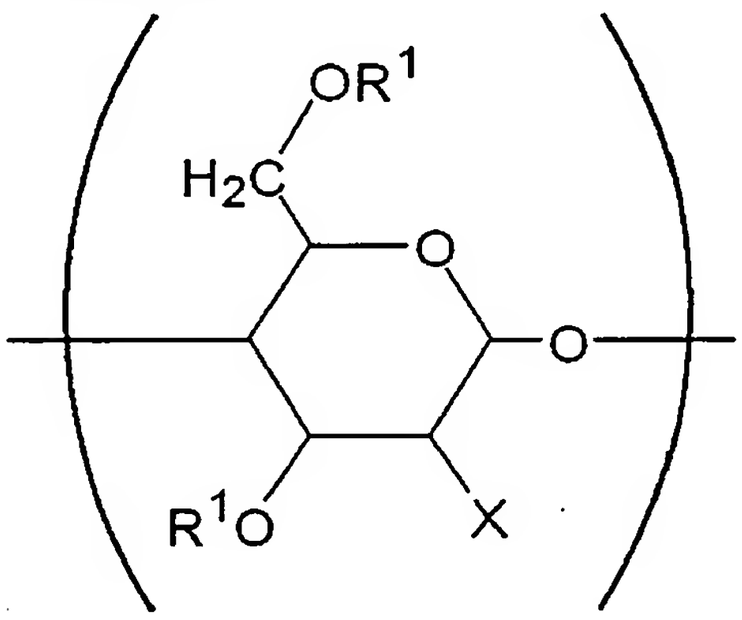
(A) Chain-like polysaccharide derivative

The chain-like polysaccharide derivative component which introduced into the side chain the succinimide residue used by this invention comes in general to introduce succinimide residue into the side chain which repeats one sort of sugar, or two or more sugar, and is included as a unit and which is guided from the hydroxyl group of sugar in a straight-line-like polysaccharide. As long as sugar forms a chain-like polysaccharide, it may not be limited, but any of homopolysaccharide or heteropolysaccharide are sufficient as it including D-glucose, D-mannose, D-fructose, D-galactose, D-xylose, D-arabinose, or these derivatives. Moreover, although association between sugar may also include branched chain, including [therefore] alpha (1->4), alpha (1->6), beta (1->4), etc., it is a straight chain-like, i.e., the molecule with which the die-length direction of a molecule may be defined clearly, in general.

[0022]

Chain-like polysaccharide derivative components are the following desirable compounds. :

[Formula 25]



(II)

It is the sugar chain included as a repeat unit, and R1 is one radical of the following four groups among a formula.

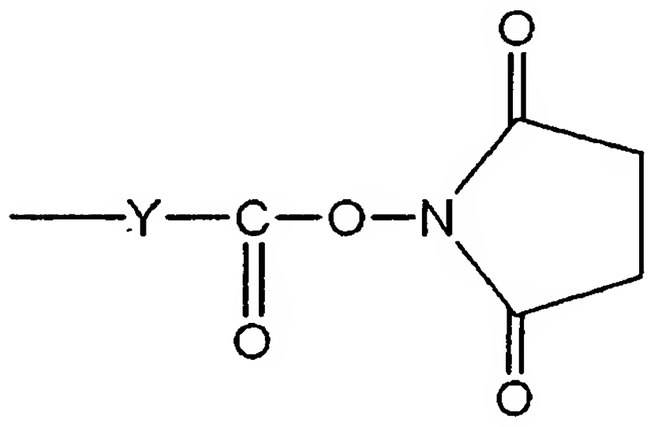
[0023]

(i) Hydrogen atom;

(ii) Aliphatic hydrocarbon and/or aromatic hydrocarbon with which a carbon number 1 thru/or 30 may be permuted;

(iii) The following type (I) :

[Formula 26]

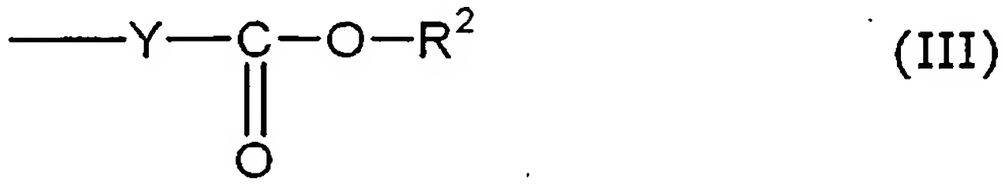


(I)

(-- Y expresses among a formula the alkylene or the carbamoyl group which may be permuted.)

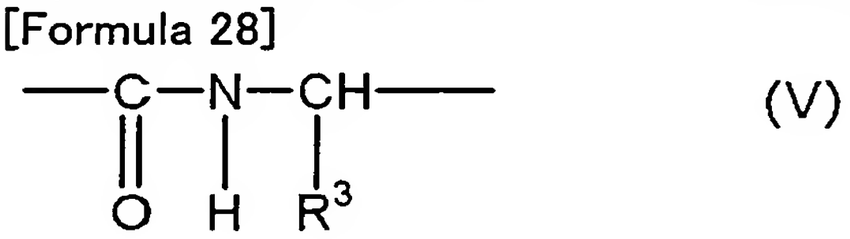
-- succinimide content radical; expressed -- and

(iv) The following type (III) :
[Formula 27]



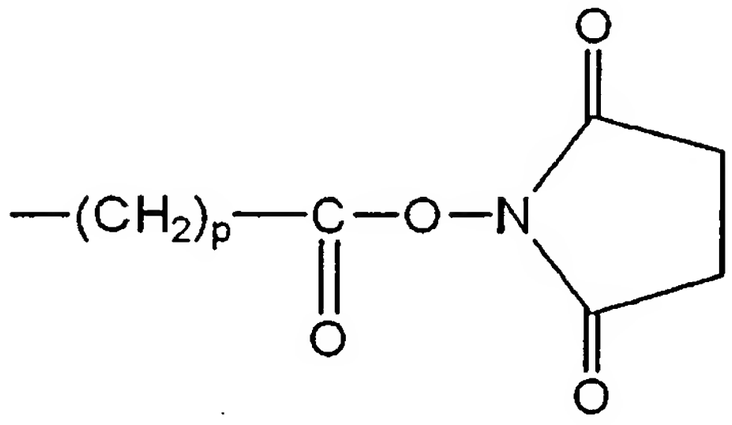
(III)

(-- Y is as having given the definition above among a formula, and R2 expresses the aliphatic hydrocarbon or aromatic hydrocarbon with which a hydrogen atom, a metal atom, a carbon number 1, or 30 may be permuted.) -- radical expressed.
[0024]
A ** (i) group is the hydroxyl group of sugar original.
A ** (ii) group etherifies or esterifies the hydroxyl group of sugar original, and includes useful various qualification. Although aliphatic hydrocarbon or especially aromatic hydrocarbon may not be limited, but a straight chain, branched chain, and annular any are sufficient as an aliphatic hydrocarbon radical and the partial saturation radical of arbitration may be included, a carbon number 1 thru/or the chain length of 30 are desirable so that the reaction of the succinimide content radical of a group (iii) may not be blocked. These aliphatic hydrocarbon or aromatic hydrocarbon may have the substituent of arbitration, unless a harmful reaction and decomposition are caused in a living body, and if chemically possible, it contains what replaced the carbon atom in a chain. Similarly, heterocycle is sufficient as a ring. As an example of such a substituent, a hydroxyl group, an oxy-radical, the amino group, a carbonyl group, a carboxyl group, a sulfhydryl group, a thioether radical, etc. are contained.
[0025]
A ** (iii) group must be a radical indispensable to an adhesion operation of this invention, therefore at least one of the R1 of a chain-like polysaccharide derivative component must be the succinimide content radical of a ** (iii) group. A ** (iv) group is the precursor.
[0026]
Therefore, Y in a ** (iii) group and a ** (iv) group is a radical which is guided from the compound which has reactivity with the hydroxyl group of a sugar chain, and does not block succinimide radical installation. Alkylene or a carbamoyl group is contained as such a radical. as alkylene -- desirable -- a carbon number 1 thru/or the alkylene of 30 -- more -- desirable -- a carbon number 1 thru/or 20 -- further -- desirable -- a carbon number 1 thru/or 10 -- they are a carbon number 1 thru/or the alkylene of 5 most preferably. A carbamoyl group is a radical expressed for example, with the following type.
[Formula 28]

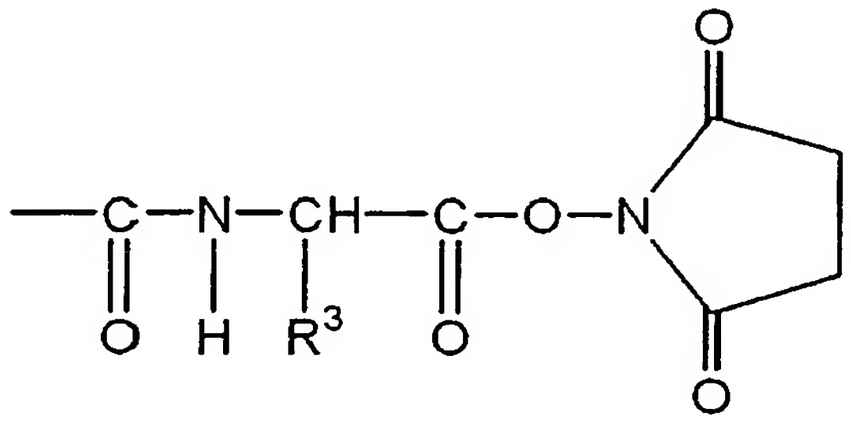


(V)

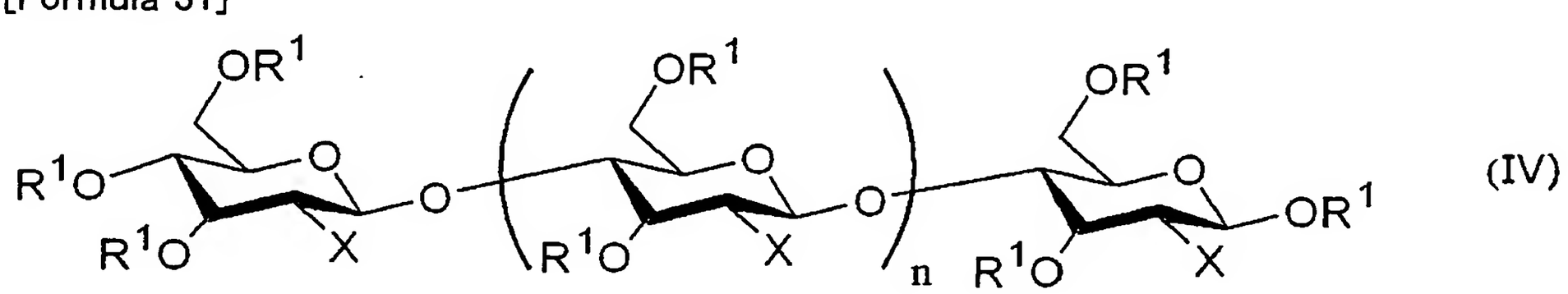
[0027]
R3 expresses among a formula the aliphatic hydrocarbon or aromatic hydrocarbon with which a hydrogen atom, a metal atom or a carbon number 1 thru/or 30 may be permuted like said R2. Therefore, it is a succinimide content R1 set desirable example,
[Formula 29]



(-- the inside of a formula, and p -- integer) of 1-5,
[Formula 30]

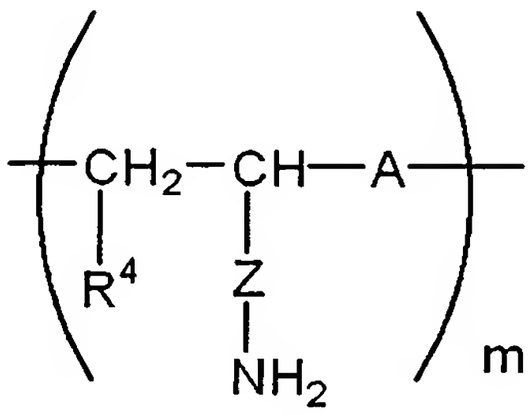


It comes out and the radical expressed is mentioned. Among a formula, although R3 is the same as said definition, it is desirable for -NHCH(R3) COO- to be a radical originating in the so-called essential amino acid and its so-called derivative used commonly. In addition, as an essential amino acid here, a glycine, an alanine, an arginine, an asparagine, an aspartic acid, a cysteine, a cystine, glutamic acid, a glutamine, a histidine, a lysine, a leucine, an isoleucine, a methionine, a phenylalanine, a proline, a valine, a thyrosin, threonine, a tryptophan, a serine, etc. are mentioned, and a hydroxyproline, hydroxylysine, etc. are mentioned to the derivative used commonly. Moreover, X is -OR1, -NHR1, or a carbamoyl group among a formula (I), and R1 and a carbamoyl group are the same as that of the above-mentioned definition among a formula.
[0028]
A chain-like polysaccharide derivative is the sugar chain of the following formula (IV) preferably.
[Formula 31]



(IV)

R1 and X are as said definition among a formula, and n is three or more integers. According to the class of X, they are a cellulosic (-OR1), a chitosan derivative (- NHR1), or a chitin derivative (carbamoyl group).
[0029]
(B) Polyamine
Polyamine is a degree type which has an amino group in a side chain although it has two or more amino groups and polyalkylene polyamine, such as ethylenediamine and diethylenetriamine, can also be used into a molecule. :
[Formula 32]



(VIII)

(R4 is a hydrogen atom, a carbon number 1 or ten alkyls, phenyl, or benzyl among a formula.) They are a carbon number 1 thru/or six alkylenes preferably. Z -- single bond or a carbon number 1 thru/or ten alkylenes -- A Single bond or hydroxy ** carboxy, a halogen, alkoxy ** one or more the oxy-radicals or amino groups which were combined by the carbon number 1 thru/or ten alkylenes, or alkylene which may be permuted by amino or the aryl group are expressed, m is two or more integers and R4 and Z may differ from A for every above-mentioned unit. It is desirable. In addition, in the polyamine of a formula (VI), end groups are alkyl groups, such as a hydrogen atom or methyl.

[0030]

As an example of such a compound, the polyvinyl amine whose R4 is a hydrogen atom, whose Z is single bond and whose A is single bond, and the poly allylamine whose R4 is a hydrogen atom, whose Z is methylene and whose A is single bond are mentioned. The with a molecular weight of about 2000 to 5000 poly allylamine is used still more preferably about 1000 to 8000 molecular weight more preferably 500 or more molecular weight. The increment in gel strength takes time amount to molecular weight less than 500, and the engine performance as a charge of a binder is inferior. Viscosity becomes it large that molecular weight is excessive, and there is a problem that handling nature falls.

[0031]

(C) Gelation reaction

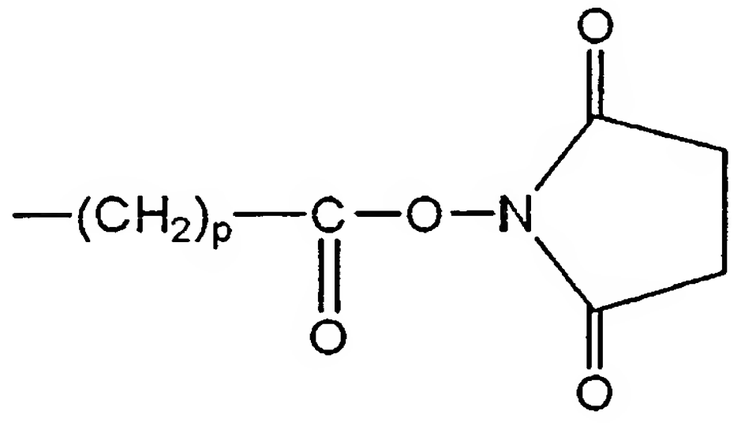
Make into an object side with ** one side of the 2nd liquid containing the 1st liquid containing the chain-like polysaccharide derivative which introduced succinimide residue into the side chain, or polyamine, and subsequently to said object side, although the multistory applying method make the liquid of another side gel ** and by being dropped and producing a gel resultant is usual In adhesion, the second page applying method which applies the 1st liquid (the 2nd liquid) to either connection or the affected part which should be carried out anastomosis, and applies the 2nd liquid (the 1st liquid) to another side may be used. Or the mixed applying methods, such as the approach of trickling the 2 above-mentioned liquid into coincidence or a spray method, etc. can be used.

[0032]

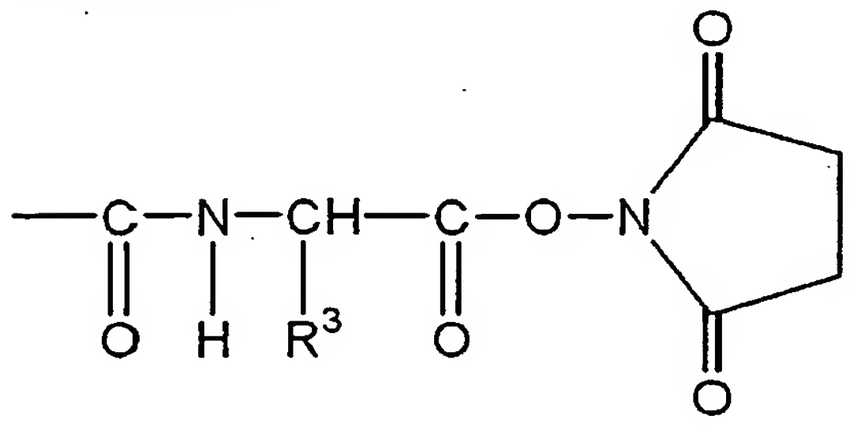
Even if it remains as it is, it can use, but generally, since viscosity is high, it may dilute and a succinimide radical content chain-like polysaccharide derivative may be used. Although especially the solvent used for dilution is not limited, when use in the living body or contact to a body tissue is taken into consideration, an aquosity solvent especially water, diluted ethanol, etc. are desirable. usually, 1 - 75 mass % extent -- desirable -- two to 60 mass % -- more -- desirable -- three to 30 mass % -- it dilutes to 4 - 20 mass % most preferably. moreover -- the case where it applies to the large range especially although the 2nd liquid containing polyamine also comes out as it is and can be used -- an aquosity solvent especially water, diluted ethanol, etc. -- usually -- 1 - 75 mass % extent -- desirable -- two to 60 mass % -- it is more preferably desirable three to 30 mass % and to dilute and use for 4 - 20 mass % most preferably. The salts of the arbitration of the range which does not do damage to a reaction may also be included, for example, pH may be adjusted with phosphate, citrate, carboxylate, etc. suitable pH -- the neutral regions 6.5-pH 7.7 -- it is pH 7.3-7.6 more preferably.

A gelation reaction is fundamentally considered to be the crosslinking reaction (accompanied by the desorption of N-hydroxysuccinimide in this case.) to which two or more amino groups in a

polyamine molecule react with the edge carbonyl group (YCO of a formula (I) carbonyl group in ...) of two or more polysaccharide derivative molecules.
[0033]
(D) The manufacture approach
The medical-application constituent of this invention consists of a chain-like polysaccharide derivative component which introduced succinimide residue into the side chain substantially as mentioned above, and polyamine. According to the suitable type of succinimide residue, the chain-like polysaccharide derivative component which introduced succinimide residue into the side chain is the following, and can be made and manufactured.
[0034]
That is, it is a succinimide content R1 set desirable example,
(a):
[Formula 33]



(-- the radical as which p is expressed in integer) of 1-5 among a formula
(b):
[Formula 34]



(-- R3 is the same as said definition among a formula.) -- although the radical expressed is mentioned, it converts into -O(CH2) pCOOH by the approach of at least one common use to hydroxyl-group-OH of a polysaccharide, or this is made to react with N-hydroxysuccinimide using a commercial carboxylation polysaccharide in (a)
[0035]
Generally the esterification reaction between a carboxylation polysaccharide and N-hydroxysuccinimide can be performed in a water solution. Although the quantitative ratio of a polysaccharide and N-hydroxysuccinimide is based on the amount of the carboxyl group contained in a polysaccharide, N-hydroxysuccinimide 0.25 mols or more is usually used for it to a carboxyl group.
Moreover, the esterification reaction between a carboxylation polysaccharide and N-hydroxysuccinimide is preferably performed to the bottom of existence of a water-soluble carbodiimide. An esterification reaction is notably promoted by existence of a water-soluble carbodiimide.
[0036]
As a water-soluble carbodiimide in this invention, a 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, 1-cyclohexyl-3-(2-mol HORINIRU-4-ethyl) carbodiimides, these hydrochlorides, or

a sulfonate can use it preferably, for example. Although especially the reaction time of an esterification reaction is not limited, for [1 minute] - 3 hours are desirable. Moreover, although especially reaction temperature is not limited, either, 0-40 degrees C is desirable. In addition to a water-soluble carbodiimide, an ester compound is generated still more efficiently by making it react to the bottom of existence of 1-hydroxyl benzotriazol (HOBt). The addition of a fusibility carbodiimide and/or 1-hydro KISHIRU benzotriazol (HOBt) is equimolar extent.

[0037]

Moreover, in the above (b), it can manufacture by various approaches, but typically, it is the hydroxyl group of a polysaccharide first. - It is -OCONHCH(R3) COOR5 (R3 is the same as said definition.) in at least one of OH. R5 is a radical similarly defined as R3. After converting and considering as a polysaccharide amino acid carver mate derivative, it is desirable to deesterify this and to make it esterify further between N-hydroxysuccinimide.

[0038]

The manufacture approach of a polysaccharide amino acid carver mate derivative is indicated by the application for patent No. 89565 [2002 to] by this invention persons. That is, the amino acid ester isocyanate expressed with OCN-HCH (R3) COOR5 is made to react with a polysaccharide under existence of a lithium chloride etc. Here, amino acid ester isocyanate is alanine ester isocyanate etc., and an amino acid part can use the aforementioned essential amino acid of passage versatility, and the derivative of the common use. But the manufacture approach of a polysaccharide amino acid carver mate derivative is not limited to the approach of an application for patent [No. 89565 / 2002 to] publication.

For example, in a dilute-alkali water solution, the deesterification reaction of a polysaccharide amino acid carver mate derivative can make a rare sodium-hydroxide water solution, a rare potassium-hydroxide water solution, etc. able to act, and can be performed. The esterification reaction between the carboxylation polysaccharide after a deesterification reaction and N-hydroxysuccinimide is the same as that of the above, and, generally can be performed in a water solution. Although the quantitative ratio of a polysaccharide and N-hydroxysuccinimide is based on the amount of the carboxyl group contained in a polysaccharide, N-hydroxysuccinimide 0.25 mols or more is usually used for it to a carboxyl group. Moreover, an ester compound is efficiently generated by making it react to the bottom of existence of a fusibility carbodiimide and/or 1-hydroxyl benzotriazol (HOBt) like the above.

[0039]

As shown in a below-mentioned example and the below-mentioned example of a comparison, if the succinimide esterification polysaccharide obtained by the above-mentioned manufacture approach remains as it is, it reacts with polyamine and does not show good gelation. However, it became clear by dialyzing succinimide esterification polysaccharide that a reaction with polyamine advanced quickly and it could use as adhesives. The rapid gelation reaction with the polyamine by dialysis of such succinimide esterification polysaccharide is not known conventionally.

[0040]

Although dialysis can be performed according to the conditions of common use, it is desirable about a 2 hour -3 day room and to carry out by applying a grade for one - two days preferably, for example using with a transparency molecular weight of 14000 or less permeable membrane. Especially suitable dialysis can be performed by exchanging distilled water for every predetermined time (for example, 1 hour) among distilled water at a room temperature.

[0041]

(E) The candidate for application

The medical-application gelation ingredient of this invention can be widely used for adhesion of an organization, junction, covering, reinforcement, a blockade, separation (adhesion prevention), etc. as above-mentioned. An organization includes artificial structure, such as an artificial blood vessel, further including the organization of the arbitration of the body and an animal. It can more specifically use as a biobinding agent aiming at adhesion of the organization of pasting of adhesion of adhesion of a dura mater, the peritoneum, a fascia, and a pleura, a bone, or a cartilage, adhesion of the parenchymatous organ incision section, adhesion of the skin, nerve

anastomosis, the microvascular anastomosis, intestinal tract anastomosis, tubal anastomosis, the skin graft, or a wound dressing etc. Moreover, since the medical-application gelation ingredient of this invention forms gel in the bottom of moisture existence like blood and body fluid and a high adhesive property is shown to a body tissue The hemostasis material aiming at hemostases, such as bleeding from the microvessel of a parenchymatous organ, and bleeding from the suture hole at the time of a suture, It can use as closing material of the living body aiming at exsorption prevention of body fluid, such as cerebrospinal fluid and bile, closing of an eardrum deficit, closing of synthetic vascular graft, closing of the air leak hole after a lung operation, closing of a bronchial tube, and the seal of a shunt tube, or a medical ingredient etc. It is useful also as prevention material of the postoperative adhesion during the organization furthermore separated by the surgical operation.

[0042]

[Example]

Hereafter, although an example and the example of a comparison explain this invention concretely, these do not limit this invention. In addition, in the following examples, "whenever [permutation]" is whenever [permutation / of the sugar chain hydroxyl group computed from the result of elemental analysis].

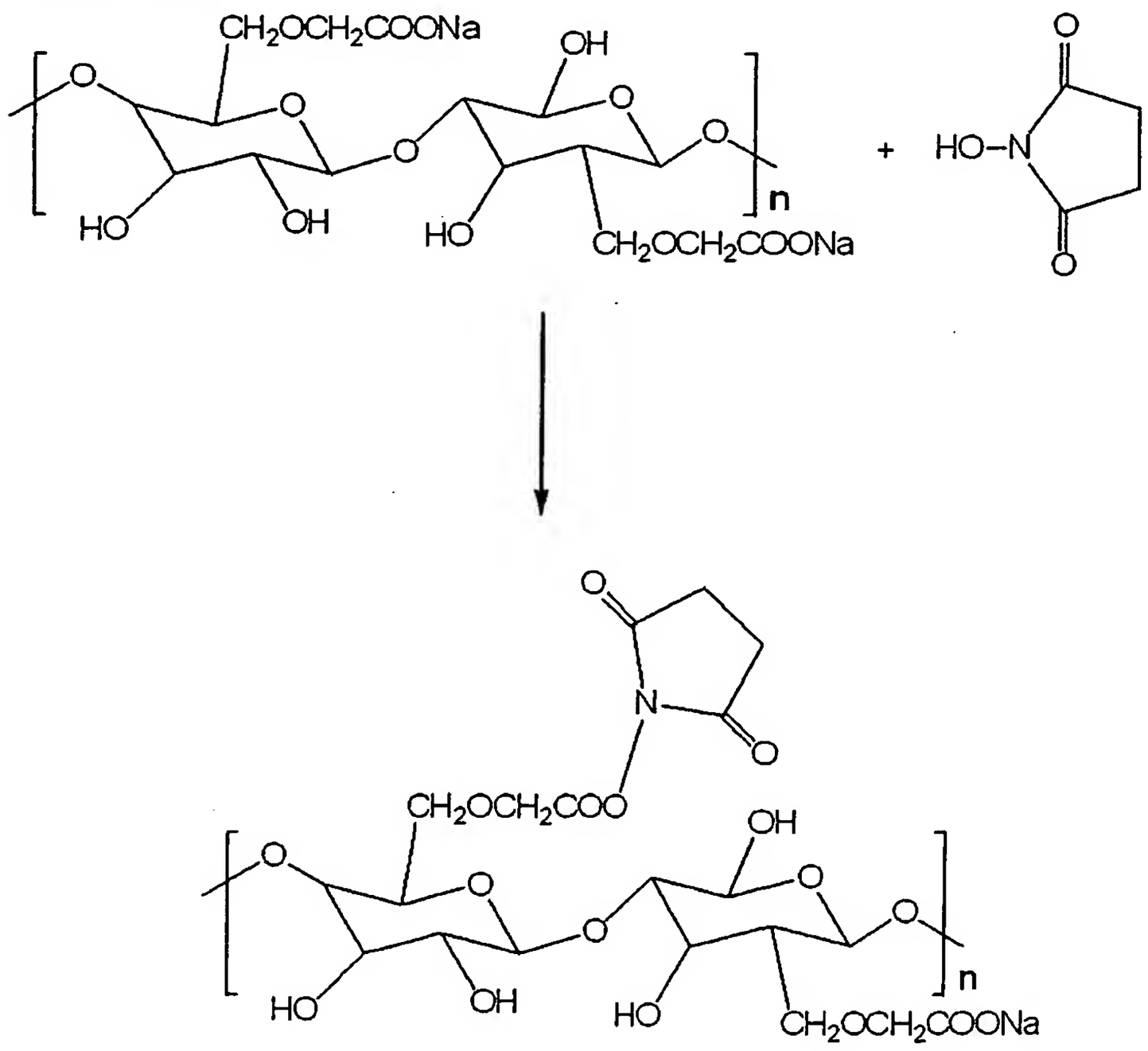
[0043]

Example 1: Composition of carboxymethyl-cellulose succinimid ester

Carboxymethyl-cellulose succinimid ester was manufactured by the reaction typically shown by the degree type (although the acetyl group guided to the 6th place is esterified in addition 1/2 by the degree type, this is for on [of explanation] expedient and it is not necessarily shown that a reaction advances at this location and rate.).

[0044]

[Formula 35]



[0045]

The carboxymethyl cellulose (1.2 whenever [2.58g and permutation] Aldrich) was melted in

water (40ml), N-hydroxysuccinic acid imide (1.16g, pure chemistry company make), 1-hydroxy benzothoria sol (1.35g, Kanto chemistry company make), and 1-ethyl-3- (3-dimethylaminopropyl-carbodiimide) (1.5514g, made in a peptide lab) was put in, and it agitated for 150 minutes at the room temperature. The product was dialyzed in two days and in distilled water in permeable membrane (the transparency molecular weight 14,000, Sanko Junyaku make) after reaction termination. After dialysis, it freeze-dried and carboxymethyl-cellulose succinimid ester was obtained (2.07g). The solubility of a product is shown in Table 1.

[0046]

[Table 1]

H_2O	MeOH	EtOH	アセトン	CH_2Cl_2	$CHCl_3$
○	○	×	×	×	×
DMSO	1,4-DO	PC	EC	DMI	
×	×	×	×	×	

表中、○は室温で実質的に溶解したもの、×は実質的に不溶だったものを表わし、
各略号はＤＭＳＯ：ジメチルスルホキシド、
１，４－ＤＯ：ジオキサン、
Ｐｃ：プロピレンカーボネート、
Ｅｃ：エチレンカーボネート、
ＤＭＩ：１，３ジメチル－２－イミダゾリジノンを示す。

[0047]

The reaction was checked by the IR spectrum. That is, in the product, the absorption (1660cm-1, 1735cm-1) corresponding to the carbonyl group of a succinimide has newly appeared, and it is shown that the succinimide was introduced into intramolecular.

[0048]

(2) Gelation by carboxymethyl-cellulose succinimid ester and the poly allylamine

The carboxymethyl-cellulose succinimid ester (0.1g) obtained in the example 1 was dissolved in phosphoric-acid buffer solution (2ml, pH7.4) among the specimen bottle, and the 10 mass % poly allylamine water solution (2ml, molecular weight 15,000, Nittobo make) was added and agitated. Gel generated in an instant after addition. The generated gel is insolubility at almost all solvents. As a result of measuring water content (a dry basis, at the time [At the time of water] of mass/desiccation i.e., mass x, 100) about the obtained gel, it was 130 - 170%.

[0049]

Example 2

(1) Composition of a cellulose (L-leucine ethyl ester KABAMETO)

The cellulose (L-leucine carver mate) was manufactured according to the approach given in an application for patent No. 089565 [2002 to].

Cellulose (microcrystal cellulose powder (Merck Co. make)) 1g was added to 45ml of 1/10 (w/v) solutions of a lithium chloride/N,N-dimethylacetamide (dehydration), and, specifically, it agitated at 100 degrees C for 24 hours. L-leucine ethyl ester isocyanate 10g is added, and it was made to react for 48 hours, after cooling this to a room temperature, agitating at 100 degrees C. After cooling, the acetone of an excessive amount was filled with the reaction solution, and the reaction was suspended. Whenever [the result of elemental analysis to / permutation] was 1.6.

[0050]

(2) Composition of a cellulose (L-leucine succinimide carver mate)

TwoMNaOH water solutions were added to the cellulose (L-leucine ethyl ester KABAMETO) compounded by (1), and it agitated at the room temperature for 24 hours. Except for insoluble matter, the cellulose (L-leucine carver mate) was obtained by filtration.

Methanol: They are the above-mentioned cellulose (L-leucine carver mate) (whenever [1.01g

and permutation] 1.6) and 1-ethyl to the flask into which the mixed solvent (15ml) of distilled water =2:1 was put. - 3 -(3-dimethylaminopropyl)- The carbodiimide (0.20g) was added. It dialyzed 3 hours after using transparency molecular weight about 14000 permeable membrane in distilled water. After performing dialysis for two days, freeze drying was performed and the white solid-state was obtained (polymer yield of 1.11g). The obtained polymer was fusibility at alkaline water and a methanol, and insoluble with dimethyl sulfoxide, an acetone, a tetrahydrofuran, and chloroform. The rate of installation of a succinimide was about 50%.
The reaction was checked with 1 H-NMR spectrum. 1H-NMR(delta/ppm):4.10- 3.90 (methylene hydrogen of leucine asymmetrical carbon), 2.77 (methylene hydrogen of a succinimide), and 1.75-1.44 (methylene hydrogen and methine hydrogen of a leucine), and 0.78 (methyl hydrogen of a leucine).
[0051]
(3) Gelation using a cellulose (L-leucine succinimid ester carver mate) and the poly allylamine
Cellulose (L-leucine succinyl ester KABAMETO) 0.1g and phosphoric-acid buffer solution (2 mL, pH7.4) which whenever [permutation] was set to 1.00, and also were compounded like the above were put into sample tubing, and the 10wt% poly allylamine water solution (1mL) was dropped here. The inside of a system was gelled in an instant. Distilled water often washed the obtained white gel, and it carried out stoving in vacuum oven (yield of 0.12g). The product was insolubility at almost all solvents.
[0052]
The examples 1-2 of a comparison
Although dialysis of the obtained carboxymethyl-cellulose succinimid ester or the cellulose (L-leucine succinimide carver mate) was omitted and also gelation was tried completely like examples 1 or 2, mixture was not gelled even if it left [more than] it on the 1st.
[0053]
[Effect of the Invention]
The polysaccharides used for this invention are the derivative of a natural polysaccharide, and polyamine of the good macromolecule of biocompatibility as explained in full detail above. This new sugar chain has the following outstanding geniuses as a medical ingredient.
1) Acquisition is an ingredient compoundable [from the easy matter] with sufficient repeatability at practical cost.
2) Physical and chemical property are widely controllable by selection of a raw material or a generation method.
3) Since safe sugar is used, it is satisfactory also from the biosafety side of the product after decomposition.
Therefore, the medical-application gelation ingredient of this invention contributes to the improvement in insurance of medicine, when alternative which manufactures the existing general-purpose medical ingredient and tools, without using the ingredient of the man and the animal origin which conceives the danger of infection is made.

[Translation done.]